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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/635,808 | 08/05/2003 | Jean Rapin | 10945.105004 | 8829 |

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| EXAMINER | |
|---|---|
| CORDERO GARCIA, MARCELA M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1654 | |

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/635,808 | RAPIN ET AL. | |
| | Examiner | Art Unit | |
| | Marcela M Cordero Garcia | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/03 and 4/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims indicate administering an effective amount of a compound of formula (I), but do not point out *to whom or to what* this effective amount is being administered. Therefore the claims currently read on any kind of subject, such as snails, bacteria, inanimate matter, etc. In addition, the claims read on administering to a subject that is in need thereof (therapeutic mode) and to a subject that is *not* in need thereof, e.g., that does not have a postlesional disease of ischemic, traumatic or toxic origin (prophylactic mode).

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims read: "...$R_1$ is a residue from one of the aminoacids Phe, Tyr, Trp, Pro, which each may be optionally substituted with one or more ($C_{1-5}$) alkoxy groups, ($C_{1-5}$) alkyl groups or halogen atoms, as well as Ala, Val, Leu or Ile;". The claims are indefinite for the following reasons:

a) It is not clear what the meaning of "optional substitution" is, e.g., does it mean replacing hydrogen in the aromatic or proline rings for a different group, or does it mean modifying the amino acid residue in a different way, for example, replacing hydrogen in the aliphatic portion of the residue or replacing an atom other than hydrogen?
b) It is not clear whether Ala, Val, Leu or Ile are to be optionally substituted *within* the amino acid residues Phe, Tyr, Trp and Pro, or if they are residues that can replace $R_1$ but that should not be optionally substituted.

With respect to the art rejections below, please note the following:

Alzheimer's disease, as referenced by Kan (Eur J Med Chem, 1992) is known in the art to be associated to brain lesions (amyloid B-protein plaques) whose density correlates with the severity of the disease and whose composition is toxic for mature neurons and brain regions (see, e.g., page 565, column 2 and page 566, column 1). Therefore, based upon the reference teachings, Alzheimer's disease can be classified as a postlesional disease of toxic origin.

In addition, please note that amnesia, as referenced by http://www.smithsrisca.demon.co.uk/neuro-glossary.html (accessed online, October 4, 2004) is known in the art to be associated, inter alia, with bilateral lesions of either the hippocampal regions or the mammilla bodies, that may have originated by a mechanical or physical agent (trauma) (http://accessscience.com/, search term 'trauma', accessed online, October 4, 2004), and therefore can be classified as a postlesional disease of traumatic origin.

Ischemic heart disease may be caused, as is know in the art and referenced by Tedeshi et al. (US 6,645,518), by atherosclerotic lesions. Therefore ischemic heart disease can be classified as postlesional disease of ischemic origin.

Alzheimer's disease and amnesia are known in the art to be neurodegenerative disorders, as referenced by Henrichwark et al. (US 6,080,848).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Vandal (US 5,212,158). The instant claims are drawn to a method for the treatment of postlesional diseases of ischemic, traumatic or toxic origin, comprising administering an effective amount of a proline derivative of formula (I). A specific species for the method is, e.g., cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide. Please note that the administered subject has not been defined and therefore the claims read upon administration to a subject not affected with any of the diseases.

Vandai beneficially teaches the use of the L-proline derivatives encompassing formula (I) for the treatment of postlesional disorders of toxic origin, such as Alzheimer's disease and of traumatic origin, such as amnesia (see, e.g., abstract and claims). Vandai teaches the species cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide (see column

16, lines 13-15), and the administration of the L-proline derivative compounds to mice in order to treat amnesia (see example 9).

Therefore, the reference is deemed to anticipate the instant claims above, as drafted.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vandai (US 5,212,158). The instant claims are drawn to a method for the treatment of postlesional diseases comprising administering an effective amount of a proline

derivative of formula (I). A specific species for the method is, e.g., cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide.

Vandai beneficially teaches the use of the L-proline derivatives encompassing formula (I) for the treatment of postlesional disorders such as Alzheimer's disease and amnesia (see, e.g., abstract and claims). Vandai teaches the species cinnamoyl-glycyl-L-phenylalanyl-L-prolinamide (see column 16, lines 13-15), and the administration of the L-proline derivative compounds to mice in order to treat amnesia (see example 9). It would have been obvious to one skilled in the art at the time that the invention was made to have used the compounds and methods taught by Vandai in the treatment of postlesional diseases such as amnesia and Alzheimer's disease, since the compounds and their activity in regards to such diseases were known as beneficially taught by Vandai. The adjustment of particular conventional working conditions (e.g., the selection of specific amino acid residues for $R_1$ and $R_2$ and X alkyl type substituents, the determination of a therapeutically effective amount to treat the specific diseases and/or the mode of administration) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/635,696.

The instantly claimed invention and the invention claimed in Application '696 are both drawn to a method of treating or preventing neurodegenerative diseases and/or postlesional diseases (such as Alzheimer's disease, in both cases) comprising administering an effective amount of a proline derivative of formula (I) including the specific species cinnamoyl-L-glycyl-L-phenylalanyl-L-prolinamide. Further, the instantly claimed method encompasses and/or is encompassed by the claimed method of Application '696.

This is a provisional obviousness-type double patenting rejection.

### *Information Disclosure Statement*

The information disclosure statements (IDSs) submitted on 11/03 and 04/04 were filed after the mailing date of the application on 08/05/2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

### *Conclusion*

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcela M Cordero Garcia
Patent Examiner
Art Unit 1654

MMCG 10-2004

CHRISTOPHER R. TATE
PRIMARY EXAMINER